Clinical review

Regular review

Bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease

Paul Brown

It is sometimes forgotten that in the story of bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease there is but one incontestable fact, that bovine spongiform encephalopathy is the cause of variant Creutzfeldt-Jakob disease. First suggested by their temporospatial association and the distinctive features of variant Creutzfeldt-Jakob disease, the link has since been proved by their equally distinctive and shared biological and molecular features.[1–3] All the rest is speculation, more or less plausible according to the arguments advanced and the absence of any satisfactory alternative explanations.

From an epidemiological point of view bovine spongiform encephalopathy has been a classic epidemic and will undoubtedly become a textbook example for students (fig 1). From economic, political, and medical points of view it has been an unmitigated disaster. Why did it begin when it did, and how did it happen?

Summary points

- The infectious agent that causes scrapie in sheep crossed the species barrier to bovines to cause bovine spongiform encephalopathy
- Changes in the rendering of livestock carcases allowed infectivity to survive and contaminate meat and bone meal in livestock feed, amplifying infection to epidemic proportions
- Export of contaminated meat and bone meal and live cattle incubating the disease caused the spread of bovine spongiform encephalopathy to other countries
- Bovine spongiform encephalopathy caused variant Creutzfeldt-Jakob disease, most probably through adulteration of cooked meat products with mechanically recovered meat contaminated by compressed spinal cord and paraspinal ganglia
- International regulatory measures are limiting the further spread of bovine spongiform encephalopathy, its entry into the human food chain, and potential secondary human to human spread of variant Creutzfeldt-Jakob disease, so that both diseases should gradually disappear

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Origin of bovine spongiform encephalopathy: recycled scrapie

The first case of a cow with bovine spongiform encephalopathy was diagnosed in 1986, and because of the long incubation periods that are characteristic of the transmissible spongiform encephalopathies—scrapie, for example, has an incubation period of about three years—the moment of infection can be assumed to have occurred years earlier. Was this just a chance occurrence, or was there some kind of environmental event that led to the infection?

The theory favoured by most scientists who have studied the disease is that it originated from an infection by scrapie in sheep. It began in the United Kingdom and not elsewhere because of a comparatively high incidence of scrapie in UK sheep and a comparatively large proportion of sheep in the mix of carcases rendered for animal feed for livestock.[4] It began in the mid-1980s because of the elimination several years earlier of a step in tallow extraction from rendered carcases that allowed some tissue infected with scrapie to survive the process and to be recycled as cattle adapted scrapie or bovine spongiform encephalopathy.[5]

Experiments to test the point with brain tissue infected with scrapie or bovine spongiform encephalopathy showed that the inactivation produced by the tallow extraction step (organic solvents and steam) was not very impressive—on average only about 10 median lethal doses (1 log LD_{50}) per millilitre.[6] Nevertheless, if infectivity was present at a concentration of less than 1 log LD_{50}/ml before tallow extraction, which seems highly probable, then the elimination of a step that had caused a one log reduction might well have been sufficient for infectivity to survive the process and contaminate the resulting meat and bone meal feed.

The probability of an input of infectivity considerably lower than 1 LD_{50}/g in the carcases coming to a rendering plant can be appreciated by some simple arithmetic. The weight ratio of carcases to processed meat and bone meal is around 5 to 1. Thus, an input of infectivity of 1 LD_{50}/g would be concentrated into 0.2 g

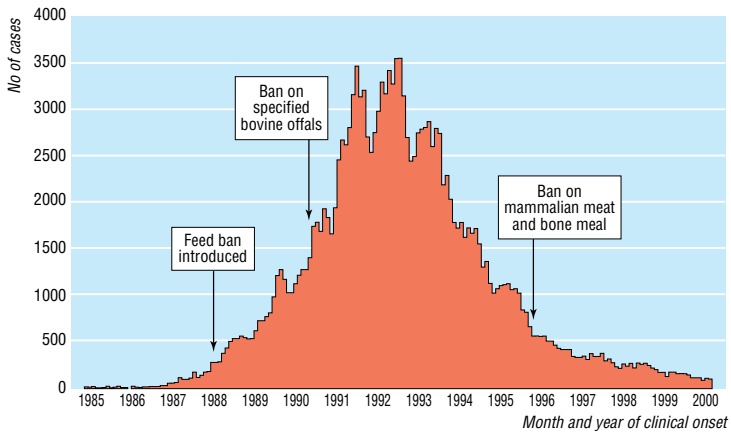

Fig 1 Chronology of epidemic of bovine spongiform encephalopathy in United Kingdom, 1986-2000

of meat and bone meal. A growing calf consumes about 2 kg of feed daily, of which meat and bone meal constitutes 4.5% by weight, or 90 g of meat and bone meal, containing 450 LD_{50}. Because 1 LD_{50} is defined as the amount of infectivity with a 50% probability of killing an animal, and even taking into consideration the effects of the different species and route of infection in natural versus experimental bovine spongiform encephalopathy, it could be reasonably surmised that a daily intake of 450 mouse intracerebral LD_{50} would have very likely killed every calf in the United Kingdom years ago.

Another feature of the scrapie hypothesis that requires explanation is that if bovine spongiform encephalopathy is caused by scrapie, and epidemiological evidence gathered over the past 50 years indicates that scrapie does not infect humans, why does bovine spongiform encephalopathy infect humans? The explanation is that when a strain of transmissible spongiform encephalopathy moves from one species to another it may acquire an altered host range—that is, scrapie in its passage through cattle could have acquired the ability to infect humans even though in its natural host it is not pathogenic. The phenomenon is unpredictable, but precedents are well known: passage of mouse adapted strains of scrapie through hamsters changes the susceptibility to disease on further passage through mice or rats; human strains of kuru or Creutzfeldt-Jakob disease do not transmit to ferrets or goats unless first passaged through primates or cats, and bovine spongiform encephalopathy does not transmit to hamsters until passaged through mice.[7–9]

Smoke and mirrors

An alternative theory, favoured by the recently completed inquiry into bovine spongiform encephalopathy, is that bovine spongiform encephalopathy was a chance occurrence resulting from a case of spontaneous disease in a cow (perhaps because of a random mutation) and that the existence of scrapie was irrelevant.[10] Although it is conceivable that spontaneous disease could be occurring in mammalian species such as cattle at about the same one per million per year incidence as sporadic Creutzfeldt-Jakob disease in humans, the theory evades the need to explain the timing and human pathogenicity of bovine spongiform encephalopathy. Specifically, it ignores the fact that indigenous bovine spongiform encephalopathy has not occurred in any other country that raises cattle and in consequence requires us to assume that spontaneous (or mutation induced) bovine spongiform encephalopathy has mysteriously chosen the United Kingdom as its only geographical site and the early 1980s as its only historical occurrence.

Other theories about the origins of bovine spongiform encephalopathy are rather too fanciful to credit seriously. For example, the idea that bovine spongiform encephalopathy results from exposure to organophosphates[11] fails to account for experimental transmissibility of the disease and for the absence of bovine spongiform encephalopathy in countries that use organophosphates extensively, such as Japan. The riposte that organophosphates originally induced a toxic disease in UK cattle that then became infectious simply has no biological (or logical) precedent. The suggestion that a soil living species of aerobic bacteria (*Acinetobacter calcoaceticus*) might have some pathogenetic importance for bovine spongiform encephalopathy, based on the finding of specific serum IgA antibodies,[12] ignores the fact that no common bacterial species even comes close to having the resistance to chemical and physical attack shown by the causative agents of transmissible spongiform encephalopathies, including bovine spongiform encephalopathy. Continuing doubts about the spread of bovine spongiform encephalopathy by contaminated meat and bone meal are demolished by the fact that it was the ban on meat and bone meal introduced in 1988 that was clearly responsible for halting the further spread of bovine spongiform encephalopathy.[13]

The origin of variant Creutzfeldt-Jakob disease

The second phase of the bovine spongiform encephalopathy story is its passage from bovines to humans in the form of variant Creutzfeldt-Jakob disease. In cattle with bovine spongiform encephalopathy the only tissues outside the central nervous system that have been shown to be infectious are the retina, the trigeminal and paraspinal ganglia, the distal ileum, and (perhaps) the bone marrow.[14] In particular, muscle and milk do not contain detectable infectivity in cattle with bovine spongiform encephalopathy or any other natural transmissible spongiform encephalopathy, including kuru, Creutzfeldt-Jakob disease, and scrapie. Therefore, beef and milk, which by virtue of the magnitude of their consumption would have been the leading candidates as vehicles for human infection, are in fact free of risk. The collection and processing of milk does not involve any steps that are vulnerable to contamination by infectious tissues, so dairy products as a group can also be considered free of risk.[15–17] However, the collection and processing of beef does involve steps in which contamination by tissue from the central nervous system could occur, and thus beef products are, by a process of elimination, the principle remaining candidates as a source of human infection.

The major suspect for the contamination of beef products is mechanically recovered meat, which is a kind of paste derived from compressed carcases from which all other consumable tissues have been manually removed. The carcases would have included intact vertebral columns with their encased spinal cords and paraspinal ganglia until December 1995, when they were prohibited from inclusion in mechanically recovered meat (in the United Kingdom). This product was legally defined as meat and was permitted to be included in most cooked meat products, such as hot dogs, sausages, meat pies, tinned meats, luncheon meats, and precooked meat patties. Other possible sources of contamination from the nervous system (for example, brain emboli induced by cranial stunning at slaughter or cross contamination of slaughterhouse tools) pale to insignificance compared with the contaminating potential inherent in this practice.

Probably the single most puzzling feature of variant Creutzfeldt-Jakob disease has been its preference for youth (fig 2). In view of the probability of beef products being the vehicle of infection, it would be facile to suppose that these comparatively popular and inexpensive items might be disproportionately present in foods for children and adolescents without far better documentary evidence than is now available. At the very least there is no indication of any socioeconomic bias in the case distribution of variant Creutzfeldt-Jakob disease. Possibly we are instead seeing an unusual (but by no means unique) example of the preference for a given disease for a given age group as a result of mixed genetic and environmental factors that baffle our understanding. We still cannot explain, for example, why the influenza virus of 1918 showed such an uncharacteristic preference for young adults or why equine encephalitides favour very young and elderly people.

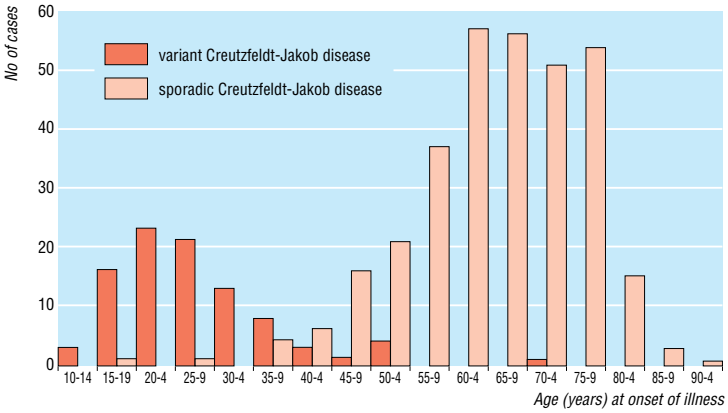

Fig 2 Comparison of ages at onset of illness in patients with variant Creutzfeldt-Jakob disease and sporadic Creutzfeldt-Jakob disease in United Kingdom, 1994-2000. Data provided by Dr Robert Will, CJD Surveillance Unit, Edinburgh

Predictions and precautions

What is in store for the future? Uncertainties still surround the issues of whether bovine spongiform encephalopathy will become endemic as a result of lateral or maternal transmission, whether it will "back cross" into sheep, carrying its newly acquired ability to infect humans (and become a disaster for the sheep industry in the absence of a practical test to distinguish it from scrapie), and to what extent it will flourish in continental Europe. The so far exclusive occurrence of variant Creutzfeldt-Jakob disease in humans who are homozygous for methionine at codon 129 of the "prion" gene may indicate either that only the 40% of normal people who carry this genotype are susceptible to infection or that other genotypes have a longer incubation period and will only become ill in the years ahead.

Uncertainty also exists about the possibility that human cases of variant Creutzfeldt-Jakob disease that are "silently" incubating may be capable of producing secondary lateral transmissions as a result of cross contamination of instruments used in surgical and invasive medical procedures or from donations of blood, tissue, or organs. The possible risk from blood has already altered the international movement of blood products and led many countries to establish deferral policies for donors who have visited or lived in the United Kingdom or continental Europe. The more difficult issues of deferrals for tissue or organ donors and precautions against instrument contamination are under scrutiny but have not yet resulted in any policy guidelines or regulations.

Optimists can take heart in the latest case predictions for variant Creutzfeldt-Jakob disease, which have plummeted from 100 000 or more cases originally suggested as a maximum estimate. Based on the yearly incidence of variant Creutzfeldt-Jakob disease in the United Kingdom through 1999, and assuming an average incubation period of between 20 and 30 years in patients presently incubating the disease, mathematical modeling now predicts an eventual upper limit of not more than about 3000 cases, and only about 600 cases if, as seems entirely reasonable, the average incubation period is less than 20 years.[18] We can also take comfort from the fact that bovine spongiform encephalopathy is trailing down to extinction in the United Kingdom and still remains a comparatively trivial problem in continental Europe, even in those countries in which active surveillance has begun to reveal increasing numbers of cases that, by virtue of inadequate warning of the general public, have produced an atmosphere of panic. In consequence, there is small likelihood of any major numbers of cases of variant Creutzfeldt-Jakob disease occurring in the population of continental Europe or among its visitors.

Nor would the exportation of most products containing ingredients of bovine origin seem to pose a major risk. The severely restricted distribution of infectivity in tissues from cattle with bovine spongiform encephalopathy coupled with reductions in infectivity through processing and dilution would in most cases reduce infectivity, even if present, to negligible levels. Thus concerns about bovine gelatine and tallow and their almost ubiquitous derivative products are directed to a risk that is more perceived than real but nevertheless carries important economic and political consequences. Indeed, the story of bovine spongiform encephalopathy and variant Creutzfeldt-Jakob disease will, as the inquiry shows, furnish a rich vein of ore to be mined by scientists, governments, and the media when faced with future

prospects of epidemic disease in animal or human populations.[19]

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A memorable patient

The evidence and Audrey

This is a tale of two extraordinary people, one a professor of evidence based medicine, the other a retired schoolteacher with advanced ovarian cancer. I was a house officer to the famous professor when Audrey, the teacher, was an inpatient under our care.

One night, although not on call, I was still tidying things up on the wards when I heard someone call my name. Looking up I saw Audrey beckoning me. She had been suffering from pneumonia arising from a metastasis of the lung, and I assumed she was asking me for some assistance. As I approached, however, she told me breathlessly that I worked too hard, I wasn't being paid for it, and that I should go home. She was that sort of person.

Audrey recovered from her pneumonia but was readmitted a week later with a massive gastrointestinal bleed. Endoscopy showed extensive, untreatable duodenal metastases. When I told the professor about Audrey, he suggested setting a transfusion limit for what was a battle that we would inevitably lose. At her bedside he explored Audrey's understanding of the situation, encouraging her to use the word "cancer." He began to enquire whether she would really want to have further transfusions, given the extent of her cancer. Audrey interrupted and asked him whether the transfusions would make her live longer. He told her that they would, but only for a very short time. Audrey said she would like them anyway.

The professor spoke to me away from the bed. The evidence was that Audrey would keep bleeding, that her cancer was end stage, and that the blood, a limited resource, would be better used for other purposes. "That blood could be used to help critically ill babies," said the professor. "What do you want to do?"

I thought about it and then said, "I don't know the babies, but I do know Audrey." My duty was to her, and I would give her the blood if she wanted it. The professor looked at me and said, "Well, I don't agree with you on this one, but I'm going to back you anyway."

Later that night Audrey changed her mind and asked for the transfusions to stop. The next morning she had another massive bleed. She was barely breathing and her family lived 45 minutes away. While waiting for them to arrive, I held on tightly to her hand and tried to pretend I wasn't crying.

The last time I saw Audrey was when I certified her dead. I talked to her gently as I listened to her chest and shone a light in her eyes, saying my medical and my real goodbyes.

Five years have passed, and Audrey has gone on to become almost as famous as the professor in the form of a conundrum on the evidence based lecture circuit (*Lancet* 1997;349:570). Ideological opinions have ranged from gross mismanagement at the expense of society, through to the importance of preserving life regardless of the cost.

Their fame is well deserved; it was a remarkable night. Even now, if a consultation is going badly Audrey's ghost may make me stop and listen to what the patient really wants. If what they want is unconventional and I'm trying to steer them round, sometimes I find myself recalling the professor. At that point, even if I don't agree with the patient, I usually back them anyway.

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We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.